



5730 5000 5638 09/869,264-10901502 PC
533 Rec'd PCT/PTO 13 AUG 2001

PATENT
Customer No. 22,852
Attorney Docket No. 1197-226

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Shinji Aki et al.

Application No.: 09/869,264

Filed: June 27, 2001

For: Process for Producing Carbostyryl
Derivatives

)
)
) Group Art Unit: Not Yet Assigned
)
) Examiner: Not Yet Assigned
)
)
)
)
)
)

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to the examination of the above application, please amend this application
as follows:

IN THE SPECIFICATION:

Page 3, replace the paragraph beginning on line 2 with the following new
paragraph:

According to the above-mentioned known process, the yield of the compound of
general formula (I) is as low as about 50 to 74%, because there is also formed a
compound in which the tetrazole derivative of general formula (III') has reacted not only
with the hydroxyl group of the carbostyryl derivative of general formula (II) but also with
the 1-position of the carbostyryl derivative of general formula (I) simultaneously. Since
the thus formed contaminative impurity is difficult to remove, production of a compound
of general formula (I) having a high purity has required a complicated process of
purification.

Page 9, replace the paragraph beginning on line 17 through page 10, line 24 with the following new paragraph:

As the phase transfer catalyst, mentioned can be made of, for example, quaternary ammonium salts substituted with a residue selected from the group consisting of straight or branched chain alkyl group having 1-18 carbon atoms, phenyl lower alkyl group including a straight or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by a phenyl group, and phenyl group, such as tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogen sulfate, tributylmethylammonium chloride, tributylbenzylammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexylammonium chloride, benzyldimethyloctylammonium chloride, methyltrihexylammonium chloride, benzylmethyloctadecanyleammonium chloride, methyltridecanyleammonium chloride, benzyltripropylammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium chloride, tetraethylammonium chloride, tetramethylammonium chloride and the like; phosphonium salts, substituted with a residue selected from the group consisting of straight or branched chain alkyl groups having 1-18 carbon atoms such as tetrabutylphosphonium chloride and the like; and pyridinium salts substituted with a straight or branched chain alkyl group having 1-18 carbon atoms such as 1-dodecanylepyridinium chloride and the like. Among these phase transfer catalysts, quaternary ammonium salts substituted with a straight or branched chain alkyl group having 1-18 carbon atoms such as tetrabutylammonium chloride and the like are particularly preferred. As the salt-forming ions in these salts, hydroxyl ion, hydrogen sulfate ion and halogen ions are preferred, among which chlorine ion is particularly

preferred. If desired, sodium sulfite or the like may be added to the reaction system of the above-mentioned reaction for the purpose of preventing the coloration caused by oxidation.

Page 11, replace the paragraph beginning on line 22 through page 12, line 13 with the following new paragraph:

Into a three-necked flask having a capacity of 300 ml were introduced 10.00 g of 6-hydroxy-3,4-dihydrocarbostyryl, 16.36 g of 1-cyclohexyl-5-(4-chlorobutyl)-1,2,3,4-tetrazole, 10.16 g of potassium carbonate, 3.00 g of tetrabutylammonium chloride, 0.05 g of sodium sulfite, 30 ml of toluene and 50 ml of water. The content of the flask was heated under reflux for 8 hours with stirring. After cooling the reaction mixture to ambient temperature, the deposited crystalline product was collected by filtration and washed with 50 ml of water. Then, the crude crystal thus obtained was introduced into 70 ml of 90% methanol cooled to 5°C, and stirred at 5°C for 10 minutes for the sake of washing. The crystal was collected by filtration and further washed on the suction filter with 20 ml of 90% methanol cooled to 5°C. The crystal was dried to obtain 21.46 g (yield 95%) of 6-[4-(1-cyclohexyl-1,2,3,4-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyryl as a colorless needle-like crystalline product.

REMARKS

The specification has been amended for clarity and to correct typographical errors. No new matter is being entered.

Support the amendment to page 3, line 9 can be found on page 4, lines 8-9. With respect to page 9, it is believed this is included within the expression "phenyl lower alkyl group." Finally, with respect to page 12, support for this can be found in Example 2, page 13, line 4.

If there is any fee due in connection with the filing of this Preliminary
Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: August 13, 2001

By: 

Arthur S. Garrett
Reg. No. 20,338

183799_1

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Application Number: 09/869,264
Filing Date: June 27, 2001
Attorney Docket Number: 1197-226

APPENDIX TO AMENDMENT OF AUGUST 13, 2001

Amendments to the Specification

Page 3, replace the paragraph beginning on line 2 with the following new paragraph:

According to the above-mentioned known process, the yield of the compound of general formula (I) is as low as about 50 to 74%, because there is also formed a compound in which the tetrazole derivative of general formula (III') has reacted not only with the hydroxyl group of the carbostyryl derivative of general formula (II) but also with the 1-position of the carbostyryl derivative of general formula [(II)] (I) simultaneously. Since the thus formed contaminative impurity is difficult to remove, production of a compound of general formula (I) having a high purity has required a complicated process of purification.

Page 9, replace the paragraph beginning on line 17 through page 10, line 24 with the following new paragraph:

As the phase transfer catalyst, mentioned can be made of, for example, quaternary ammonium salts substituted with a residue selected from the group consisting of straight or branched chain alkyl group having 1-18 carbon atoms, phenyl lower alkyl group including a straight or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by a phenyl group, and phenyl group, such as tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

hydrogen sulfate, tributylmethyammonium chloride, tributylbenzylammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexylammonium chloride, benzyltrimethyloctylammonium chloride, methyltrihexylammonium chloride, benzylmethyloctadecanilyammonium chloride, methyltridecanilyammonium chloride, benzyltripropylammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium chloride, tetraethylammonium chloride, tetramethylammonium chloride and the like; phosphonium salts, substituted with a residue selected from the group consisting of straight or branched chain alkyl groups having 1-18 carbon atoms such as tetrabutylphosphonium chloride and the like; and pyridinium salts substituted with a straight or branched chain alkyl group having 1-18 carbon atoms such as 1-dodecanilypyridinium chloride and the like. Among these phase transfer catalysts, quaternary ammonium salts substituted with a straight or branched chain alkyl group having 1-18 carbon atoms such as tetrabutylammonium chloride and the like are particularly preferred. As the salt-forming ions in these salts, hydroxyl ion, hydrogen sulfate ion and halogen ions are preferred, among which chlorine ion is particularly preferred. If desired, sodium sulfite or the like may be added to the reaction system of the above-mentioned reaction for the purpose of preventing the coloration caused by oxidation.

Page 11, replace the paragraph beginning on line 22 through page 12, line 13 with the following new paragraph:

Into a three-necked flask having a capacity of 300 ml were introduced 10.00 g of 6-hydroxy-3,4-dihydrocarbostyryl, 16.36 g of 1-cyclohexyl-5-(4-chlorobutyl)-

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

1,2,3,4-tetrazole, 10.16 g of potassium carbonate, 3.00 g of tetrabutylammonium chloride, 0.05 g of sodium sulfite, 30 ml of toluene and 50 ml of water. The content of the flask was heated under reflux for 8 hours with stirring. After cooling the reaction mixture to ambient temperature, the deposited crystalline product was collected by filtration and washed with 50 ml of water. Then, the crude crystal thus obtained was introduced into 70 ml of 90% methanol cooled to 5°C, and stirred at 5°C for 10 minutes for the sake of washing. The crystal was collected by filtration and further washed on the suction filter with 20 ml of 90% methanol cooled to 5°C. The crystal was dried to obtain 21.46 g (yield 95%) of 6-[4-(1-cyclohexyl-1,2,3,4-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyryl as a colorless needle-like crystalline product.